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Award Number: W81XWH-04-1-0884

TITLE: Radioimmunotherapy (RIT) Dose-Escalation Studies in Prostate Cancer Using Anti-PSMA Antibody 177Lu-J591: RIT Alone and RIT in Combination with Docetaxel

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REPORT DATE: October 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE 01-10-2007		2. REPORT TYPE Annual		3. DATES COVERED 15 Sep 2006 – 14 Sep 2007	
4. TITLE AND SUBTITLE Radioimmunotherapy (RIT) Dose-Escalation Studies in Prostate Cancer Using Anti-PSMA Antibody 177Lu-J591: RIT Alone and RIT in Combination with Docetaxel				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-04-1-0884	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Shankar Vallabhajosula, Ph.D. Email: svallabh@med.cornell.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Weill Medical College of Cornell University New York, NY 10021-4870				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Phase I dose escalation studies with 177Lu-DOTA-huJ591 using dose fractionation regimen will be performed in patients with PCa and who have recurrent and/or metastatic disease. The 177Lu dose (20-45 mCi/m2) will be escalated in 6 different dose levels (3-6 patients at each dose level). At each dose level, the patients would receive two doses of 177Lu-J591 Mab, 2 weeks apart. The dose of huJ591 MAb will remain fixed at a total dose of 20 mg/dose. After almost 2.5 years of discussions, the phase I protocol was finally approved in Aug 2007 by HSSRB at DOD. In January 2007, we prepared a new lot of DOTA-J591 under GMP conditions for clinical studies. After receiving the approval, we started clinical studies in August 2007. We already recruited the first 3 subjects in Group-1. We hope to complete the first trial by June 2008 and start the combination therapy protocol almost immediately. We plan to complete the study in march 2009. The revised SOW is attached.					
15. SUBJECT TERMS Radioimmunotherapy, Prostate cancer, 177Lu-DOTA-J591 antibody, Dose-Fractionation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER (include area code)

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Introduction

We still lack a systemic treatment that clearly demonstrates improved survival in patients with disseminated hormone resistant prostate cancer (PC). Targeted radioimmuno-therapy (RIT) utilizing radiolabeled monoclonal antibodies (mAbs) directed to cancer-related cell surface antigens has been clinically validated with the FDA approval of ^{90}Y and ^{131}I labeled anti-CD20 mAbs (Zevalin and Bexxar) for the treatment of lymphoma.

Metastatic PC is a rational candidate for RIT since PC is radioresponsive, and typically develops as small-volume micro-metastatic sites of disease in marrow and lymph nodes that receive high levels of mAb. In PC, the most well established, prostate-restricted, cell surface antigen yet identified is prostate specific membrane antigen (PSMA). It is an ideal target for developing therapeutic agents as it is expressed by all the PCs and the expression levels progressively increase in more poorly differentiated, metastatic and hormone-refractory prostate cancers (HRPC).

J591 is a de-immunized mAb that binds with a very high affinity to the extracellular domain of PSMA on the viable tumor cells. In addition, the PSMA-J591 antibody complex is internalized, thereby delivering any antibody payload (radioisotope or drug) to the interior of the targeted cells. We have demonstrated radiolabeled J591 sensitively and specifically targets sites of metastatic PC in both bone and soft tissue. In a Phase I studies, we have determined that ^{90}Y -J591 (17.5 mCi/m²) and ^{177}Lu -J591 (70 mCi/m²) mAbs either decrease or stabilize serum PSA levels. We have selected ^{177}Lu -J591 as an agent of choice for further studies. ^{90}Y may be appropriate for larger tumors while ^{131}I may be more cytotoxic for smaller, micro-metastatic lesions typically seen in HRPC. ^{177}Lu behaves chemically like ^{90}Y and is stable in vivo. ^{177}Lu has low energy β^- particles and suitable γ photons for dosimetric studies. Thus it has advantages of both ^{90}Y and ^{131}I , but none of their disadvantages. Therefore **^{177}Lu -J591 may be an ideal agent for RIT studies of PC.**

The degree of anti-tumor response following RIT depends on several variables, especially total (cumulative) radiation dose to the tumor, dose-rate and tumor radiosensitivity. Also, myelotoxicity is the dose-limiting factor in RIT. Therefore strategies are needed to optimize dosimetry to the bone marrow and tumor. Dose-fractionation is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose-rate. Preclinical studies strongly support this strategy. Combined modality radioimmunotherapy (CMRIT) is another strategy designed to enhance the cascade of molecular events required for apoptotic tumor cell death resulting from the continuous low dose-rate radiation. FDA approved anti-neoplastic agent docetaxel can cause microtubular dysfunction and as a result cells are blocked in the G₂/M phase of the cell cycle, thus increasing sensitivity of cells to radiation.

Therefore, **we propose to perform two independent phase I dose-escalation studies** in patients with HRPC. The first protocol is designed to determine the cumulative MTD of ^{177}Lu -J591, in a fractionated dose regimen of 2 low dose treatments given 2 weeks apart. A follow up protocol is designed to determine a safe dose of docetaxel to be given in combination with a fractionated dose regimen of ^{177}Lu -J591. This research proposal thus combines several important strategies for successful RIT of PC; a very specific and high affinity anti-PSMA mAb J591, an ideal radionuclide ^{177}Lu with useful γ and β^- energies for imaging and therapy, **dose fractionation and CMRIT strategies (with docetaxel) to reduce myelotoxicity and to augment the anti-tumor response of RIT.**

In the revised SOW attached here, we identified 4 major tasks. In the body of text, we will describe the major tasks completed. In addition, we will describe the problems and difficulties for not being to complete the remaining tasks in a timely manner.

Body of Text based on SOW

REVISED STATEMENT OF WORK (SOW) Revised on October 15th 2007

Task 1: Preparation of ¹⁷⁷Lu-DOTA-J591 mAB for clinical studies.

Under GMP conditions, monoclonal antibody HuJ591-GS Antibody was DOTA conjugated, vialled and labeled by Immunomedics Inc. which is the current manufacturer of record for the vialled DOTA-HuJ591 antibody drug product. The manufacturer's address and telephone number are:

Immunomedics Inc.
300 Americasn Road
Morris Plains, NJ 07950
Phone: 973-605-8200

The drug product consists of DOTA-HuJ591 antibody in 0.3 M ammonium acetate, pH 7.2, in 2 mL thermoplastic vials with gray butyl rubber stoppers and blue flip-off crimp seal closures. The nominal concentration is 8.0 mg/mL and the nominal fill volume is 1.3 mL. There are no other excipients added.

¹⁷⁷Lu-Labeling of DOTA-J591: 3 batches of the above lot of DOTA-J591 were labeled with ¹⁷⁷Lu to a specific activity of 10-20 mCi/mg. All the QC tests indicated that the material is suitable for clinical studies.

The above process was started around October and final tests were completed by March 2007.

Task 2: Obtain IRB approval of the Phase I dose escalation protocol using ¹⁷⁷Lu-J591 in a fractionated dose regimen

- After 16 months of interaction with HSRRB at DOD, the protocol was finally approved in May 2006. Subsequently, the protocol (modified by Cornell IRB and DOD HSRRB) was submitted to FDA for permission to start the clinical trial under an IND.
- In August 2006, the physician who is responsible for recruiting the patients and who is the PI on the institutional protocol left Cornell medical center. We subsequently replaced the physician and resubmitted the protocol for IRB approval and FDA approval.
- Finally in January 2007, we received the approval from FDA following minor modifications to the protocol as suggested by FDA.
- The revised protocol was resubmitted to Cornell IRB and then finally to HSRRB at DOD (in January 2007)
- After several communications, we were just informed that the protocol is finally approved. We are still waiting for the formal letter of approval from DOD.
- **The protocol was finally approved by HSRRB in July 2007 and clinical studies started**

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Task 3: Phase I clinical trial with ¹⁷⁷Lu-J591 Dose fractionation regimen

We have started recruitment of patient in this protocol. In the last 2-3 months, we have already recruited 3 patients and completed Group-1 of patients. We plan to start Group-2 within the next 1-2 weeks.

Our plan is complete the Phase 1 Fractionation protocol before the **end of June 2008.**

Task 4: Phase 1 Clinical trial with ^{177}Lu -J591 and Docetaxel.

We started the design of Phase 1 protocol of combination therapy. We plan to submit the protocol for by April to IRB and HSSRB for review.

The goal is start the clinical trial In July 2008 and complete the recruitment of patients before March 1st 2009.

The data analysis can be completed after the patient recruitment is finished.

Key Research Accomplishments

- Preparation of new lot of DOTA-J591 and optimization of ^{177}Lu labeling.
- Obtaining IRB approvals following repeated review of protocol by Cornell IRB, HSRRB and FDA
- Obtaining HSSRB approval for the trial
- Recruited the first 3 subjects in Group-1 of the first phase I clinical study evaluating the dose fractionation.

Reportable Outcomes

We were asked to submit abstracts for the Department of Defense “IMPact” meeting in September 2007

Three abstracts were presented based on our work on 3 grants we received from DOD since 1998.

1. ^{177}Lu -Dota-J591, a Radiolabeled Monoclonal Antibody Specific to the Extracellular Domain of Prostate Specific Membrane Antigen (PSMA): Radioimmunotherapy (RIT) Studies in Patients with Prostate Cancer (**Oral presentation**)
2. ^{90}Y -Dota-J591, a Radiolabeled Monoclonal Antibody Specific to the Extracellular Domain of Prostate Specific Membrane Antigen (PSMA): Radioimmunotherapy (RIT) Phase I Dose Escalation Studies in Patients with Prostate Cancer (**poster presentation**)

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3. Prostate Specific Membrane Antigen (PSMA): an Ideal Target for Developing Radiolabeled Monoclonal Antibodies for Diagnosis and Therapy (**poster presentation**)

Other Publications from our group on Radiolabeled J591:

1. Bander NH; Milowsky MI; Nanus DM; Kostakoglu L; Vallabhajosula S; Goldsmith SJ Phase I Trial of ¹⁷⁷Lutetium-Labeled J591, a Monoclonal Antibody to Prostate-Specific Membrane Antigen, in Patients With Androgen-Independent Prostate Cancer. J Clin Oncol 2005;20;23(21): 4591-4601
2. Milowsky MI, Nanus DM, Kostakoglu L, Sheehan CE, Vallabhajosula S, Goldsmith SJ, Ross JS, and Bander NH. Vascular Targeted Therapy With Anti-Prostate-Specific Membrane Antigen Monoclonal Antibody J591 in Advanced Solid Tumors. J Clin Oncol 2007; 25:540-547.